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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/748,789	12/22/2000	Anthony P. McHale	11067/1090	3325

29933 7590 11/20/2002

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/748,789	MCHALE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *5-8,20-29,33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 9-19 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, directed to a method of producing a red blood cell comprising an agent, cells produced and an in vitro use of the cells; and species election to a protein agent, in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 5-8, 20-29, and 33-35 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Claims 1-4, 9-19, 26, and 30-32 are under current examination.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 and 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Great Britain on August 9, 2000. It is noted, however, that applicant

has not filed a certified copy of the PCT/GB00/03056 application as required by 35 U.S.C. 119(b).

Claim Rejections

Claims 4, and 9-12 are objected to because they comprise the subject matter that read on non-elected invention. Upon election of an invention for examination, the claims should be amended so that they only read on the elected invention. Appropriate corrections are required.

Claim 32 is objected to because the abbreviation "PEG" should be spelled out the first time it appears in the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 9-19, 29, and 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pre-sensitizing the RBC with electroporation *in vitro*, does not reasonably provide enablement for presensitizing the RBC with electroporation *in vivo,* or presensitizing using an ultrasound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims embrace a method for loading red blood cell with a polypeptide agent by electroporation, wherein one aspect of the invention drawn to carrying out such loading process in vivo as evidenced by the dependent claim 9. However, the specification is silent with regard to an in vivo loading process, how to apply an electric field selectively on the population of red blood cells *in vivo* and how to delivering the agent to be loaded into the particular cells, therefore, fails to provide an enabling disclosure commensurate in scope with the claims.

The claims further embrace presensitising the RBCs with an ultrasound wave energy. However, the specification only teaches using the ultrasound for disruption of RBCs, which would lead to the release of the loaded agent (e.g. example 4). The specification is silent regarding the ultrasound energy used for presensitizing RBCs. In view of the state of the art, the art known knowledge is drawn to using ultrasound

energy to destroy cells (*Halaka*, US 6,071,480, column 1, lines 16-25; and *Mitchell et al*, Biotech Applied Biochem 1990;12:264-75, page 267). In view of such, the invention does not appear to be enabled in the absence of specific teaching and evidence to the contrary.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 18, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is vague and indefinite because the claim as written is difficult to comprehend. For compact prosecution, the claim is interpreted as loading two agents in a red blood cell. However, clarification is required.

Claim 18 is vague and indefinite because the claim recitation, "diagnostic ultrasound" or "therapeutic ultrasound". The specification fails to define the meaning of the terms, it is unclear what kind of ultrasound is considered as diagnostic or therapeutic, thus, the metes and bounds of the claims are unclear.

Claim 19 is vague and indefinite because it limits the applied ultrasound energy source by power level. First, it is unclear what kind of powers the claim embraces, e.g.

electric current or some other power source; second, different sonicator may generate different ultrasound wave frequency, thus, the same electric power level may vary depending on the sonicator used. Therefore, the metes and bounds of the claims are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (f) he did not himself invent the subject matter sought to be patented.

Claims 4, 18, 19 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by commonly assigned copending Application No. 09/748,063 which has a common inventor with the instant application.

Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application.

The present claims and claims 8-14 are each drawn to a method for selectively releasing an agent from a red blood cell comprising the step of electrosensitizing the cells and applying ultrasound to release the agent. The methods of the present

application and the cited co-pending application differ in that claims 8-14 of the co-pending application do not recite a presensitizing step, however, it is disclosed in the specification, paragraph 0196. Therefore, they are obvious variants.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

Claims 4, 18, 19 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

Claims 4, 18, 19 are claiming the same invention as that of claims 8-14 of co-pending Application No. 09/748,063. However, the cited application has a different inventive entity.

Claims 1, 3, 9, 10, 14-17, 26, 30, and 31 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

These claims are obvious variants over claims 19-21 of co-pending Application No. 09/779,186, now allowed. However, the cited application has a different inventive entity.

Claims 1, 9, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by *Mouneimne et al* (US 5,236,835).

The claims are drawn to a method of producing a red blood cell comprising an agent, comprising pre-sensitizing said red blood cell and loading the agent, wherein the sensitizing step is performed *in vitro* by applying an electric field to said RBC, wherein the agent is a protein. The specification teaches that the pre-sensitizing must perform prior to or concomitant with the loading step (specification, page 10, line 21).

Mouneimne et al teach a method of incorporating a CD4 or glycophorin into a red blood cell by applying an electric field in the presence of a solution (electroporating concomitant with loading) containing the agent to be loaded to the RBC (abstract, column 1, lines 46-54). Therefore, *Mouneimne et al* anticipate the instant claims.

Claims 1, 2, 9, 10 are rejected under 35 U.S.C. 102(b) as being anticipated by *Lizano et al* (Biochimica Biophysica Acta 1998;1425:328-336).

Claim 2 is drawn to loading two polypeptides into a red blood cell.

Lizano et al teach a method of encapsulating two types of enzymes into human red blood cells, ADH and ALDH, comprising electroporating (concomitant with loading) the RBC-enzymes mixture (Section 2.3, page 329). Therefore, *Lizano et al* anticipate the instant claims.

Claims 1, 2, 4, 9, 10, and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by *Mitchell et al* (Biotech Applied Biochem 1990;12:264-75), and as evidenced by *Halaka* (US 6,071,480).

Mitchell et al teach a method of encapsulating rIL-2 and human serum albumin into human RBC by applying electric field-pulse (page 266). They then sonicate the electroporated red cell carrier to release rIL-2 using a Branson Probe Sonifier (3rd paragraph, page 267). *Mitchell et al* do not use the term ultrasound, however, as taught by *Halaka*, the sonicator is a device for generating ultrasonic waves (column 1, lines 26-27). Therefore, *Mitchell et al* anticipate the instant claims.

Claims 1, 9, 10, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by *Zimmermann et al* (US 4,289,756).

Claim 12 is drawn to a method of loading RBCs using combination of hypotonic dialysis and eletroporation.

Zimmermann et al teach a method of introducing medicaments into cells including erythrocytes using the combination of osmotic pressure (hypotonic dialysis) and electric field (e.g. claim 1), wherein the medicament could be in the form of a protein (column 4, line 18). Therefore, *Zimmermann et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 13-17, 26, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Mitchell et al* (Biotech Applied Biochem 1990;12:264-75), in view of *Ortiz et al* (Mutation Res 1995;327:161-9).

The claims are drawn to multiple treatments of RBCs using electroporation (before or after loading), wherein the electric field applied ranges from 0.1-10 kV/cm and 1-100 microseconds, and cells produced by the process.

Mitchell et al teach that loading two proteins into RBCs by electroporation and the content release of red cells are positively linked to increased pulse length, frequency, and intensity of the electric field, they teach using a electric field ranges from 6-8 kv/cm from 5-40 microseconds. *Mitchell et al* load the two proteins at once, and do not use multiple doses of electroporation.

Ortiz et al teach a method of loading CHO cells with two (protein) enzymes using different combinations of single- and double-dose electroporation, they teach that separate loading of two enzymes as an alternative protocol for certain need, and teach that once the cells have been electroporated, they would resist a second electroporation without significant loss of cell viability (2nd paragraph, right column, page 167).

Evidently, it is known that electroporation would enhance protein loading to RBCs, that two agents could be loaded together or separately with double dose of electroporation without significant loss of viability. Accordingly, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the methods taught by *Mitchell et al*, and *Ortiz et al* by simply using the protocol of multiple doses of electroporation for loading RBCs with a reasonable expectation of success. The skilled in the art would have been motivated to do so for separate loading of agents or for easier release of loaded agent at a later time. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 3, 13-17, 26, and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Mitchell et al* (Biotech Applied Biochem 1990;12:264-75) and *Ortiz et al* (Mutation Res 1995;327:161-9) as applied to claims 1, 3, 13-17, 26, 30, 31 above, and further in view of *Magnani et al* (US 6,139,836).

Claim 32 is further drawn to a loaded RBC comprises PEG.

Magnani et al teach using PEG as pharmaceutically acceptable carriers for in vivo delivering loaded erythrocytes (column 7, line 63).

Accordingly, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the methods taught by *Mitchell et al, Ortiz et al, and Magnani et al* by simply choosing PEG as pharmaceutical carrier for *in vivo* delivery of loaded RBCs with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 3, 4, 13-17, 19, 26, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Mitchell et al* (Biotech Applied Biochem 1990;12:264-75) and *Ortiz et al* (Mutation Res 1995;327:161-9) as applied to claims 1, 3, 13-17, 26, 30, 31 above, and further in view of *Halaka* (US 6,071,480).

Claim 19 is further drawn to an applied ultrasound energy source at a power level from about 0.05-100 W/cm2.

Halaka teaches using different power levels to generate different ultrasonic wave frequency, such as at 100watts of power (column 12, line 6).

Accordingly, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the methods taught by *Mitchell et al, Ortiz et al, and Halaka* by simply choosing various power levels for content release of loaded RBCs with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 9, 10, 13, 14, 15, 16, 17, 26, 30, and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-21 of U.S. Application No. 09/779,186, now allowed. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed method in the cited patent encompasses the instant claims.

The reference patent qualifies under this provision because there is one common inventor and a common assignee between the instant application and the cited patent.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present application and the claims 19-21 of the cited patent are each drawn to a method for pre-sensitizing and loading cells using single or multiple doses of electroporation prior to or after the loading process.

The processes of the present application and the cited patent differ one from the other in that the claims of the cited patent does not particularly recite the red blood cells.

However, the RBC is one of the intended cells used in the process is fully disclosed in the cited patent (e.g. see abstract).

Therefore, the inventions as claimed are co-extensive.

Please note that because the cited patent has the same effective filing date as the instant application, it is a prior art over instant application. However, the above double patenting rejection still applies.

Claims 4, 18, 19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-14 of co-pending Application No. 09/748,063. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The reference co-pending application qualifies under this provision because there is one common inventor and a common assignee between the instant application and the cited patent.

The present claims and claims 8-14 are each drawn to a method for selectively releasing an agent from a red blood cell comprising the step of electrosensitizing the cells and applying ultrasound to release the agent. The methods of the present application and the cited co-pending application differ in that claims 8-14 of the co-pending application do not recite a presensitizing step, however, it is disclosed in the specification, paragraph 0196. Therefore, the claims are obvious variants.

Therefore, the inventions as claimed are co-extensive. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3, 9, 10, 12, 13, 14, 15, 16, 17, 26, 30, and 31 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26, 29-37 of co-pending Application No. 09/779,188. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The reference patent qualifies under this provision because there is one common inventor and a common assignee between the instant application and the cited patent.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present application and the claims 26, 29-37 of the cited patent are each drawn to a method for pre-sensitizing and loading cells using single or multiple doses of electroporation prior to or after the loading process or combined with hypotonic dialysis.

The processes of the present application and the cited patent differ one from the other in that the claims of the cited patent does not particularly recite the red blood cells. However, the RBC is one of the designated cells used in the process, and is fully disclosed in the cited patent (e.g. see abstract).

Therefore, the inventions as claimed are co-extensive.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Please note that because the cited patent has the same effective filing date as the instant application, it is ~~a~~ not prior art over instant application. However, the above double patenting rejection still applies.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
November 15, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER